SELECTIVE COX-2 INHIBITION FROM EDIBLE PLANT EXTRACTS

Cross-Reference to Related Applications

This application is a continuation-in-part of and claims priority from U.S. Application Serial No. 09/272,363, filed March 19, 1999, which is hereby incorporated by reference in its entirety.

Field of the Invention

The current invention is generally directed toward nutraceuticals that are nonsteroidal anti-inflammatory agents capable of inhibiting cyclooxygenase-2 (COX-2). The present invention relates to a method for inhibition of COX-2, or selective inhibition of COX-2, in an organism by administering to the organism organic extracts isolated from edible plants wherein such extracts inhibit COX-2 activity. The present invention also relates to purified compositions of the edible plant organic extracts. In addition, the current invention is directed toward a method for treating and/or preventing COX-2 mediated inflammation or inflammation-associated disorders in an organism.

Background of the Invention

The prostaglandins are a potent class of biologically active lipid derivatives that play a crucial role in the inflammatory response. The inflammatory response is a localized tissue response to injury or other trauma characterized by pain, heat, redness and swelling. Prostaglandins mediate this response by inhibiting platelet aggregation, increasing vascular permeability, increasing vascular dilation, inducing smooth-muscle contraction and causing the induction of neutrophil chemotaxis . Because of their central role in mediating the inflammatory response, significant efforts have been directed toward

elucidating compositions that are capable of inhibiting the biosynthesis of prostaglandins.

Toward that end, prostaglandin biosynthesis has been extensively characterized. Prostaglandins are a group of oxygenated fatty acids that are generally derived from arachidonic acid . The biosynthesis of prostaglandins from arachidonic acid occurs in a three step process that includes 1) hydrolysis of arachidonic acid from phospholipid precursors catalyzed by a phospholipase A_2, 2) cyclooxygenase ("COX") catalyzed oxygenation of arachidonic acid to prostaglandin G2 ("PGG2"). This COX catalyzed reaction is the first committed and rate limiting step in prostaglandin synthesis; and 3) conversion of prostaglandin G2 to the biologically active end product, prostaglandin, catalyzed by a series of synthases and reductases. Upon their synthesis, prostaglandins exit the cell and act in a hormone-like manner by effecting the target cell via G protein linked membrane receptors.

Inactivation of the COX enzyme is a natural target as a means to inhibit prostaglandin production due to this enzyme's pivotal role in the prostaglandin biosynthetic pathway. It is now known that two gene products possessing COX enzyme activity are expressed, termed COX-1 and COX-2. COX-1 was the first discovered isoform and is constitutively expressed in most tissue types. Because it is constitutively expressed, COX-1 is available to participate in activities requiring a rapid physiological response and causes the production of prostaglandins involved in "house-keeping" functions. For example, COX-1 is responsible for acute production of prostaglandins that regulate vascular homeostasis, maintain gastrointestinal integrity, and maintain kidney function. Thus, COX-1 activity is

responsible for the synthesis of prostaglandins required for the maintenance of several cell types.

COX-2, on the other hand, is a recently discovered isoform that is inducibly expressed in response to numerous stimuli such as bacterial lipopolysaccharides, growth factors, cytokines, and phorbol esters. In addition, COX-2 is only expressed in a limited number of cell types including monocytes, macrophages, neutrophils, fibroblasts and endothelial cells. COX-2 expression, unlike COX-1 expression, has been shown to increase in rheumatoid synovial tissue. Contrastingly, COX-2 expression is inhibited in response to glucocorticoids and by anti-inflammatory cytokines. Thus, based upon these observations, COX-2 has been shown to be the isoform responsible for mediating the production of prostaglandins that participate in the inflammatory response and inflammatory related disorders. In addition, COX-2 has also been shown to participate in certain cancers, Alzheimer's disease, atherosclerosis, and central nervous system damage resulting from stroke, ischemia and trauma.

Corticosteroids provide one means to reduce effects associated with the inflammatory response. These potent anti-inflammatory agents exert their effect by causing a reduction in the number and activity of immune system cells via various mechanisms. However, prolonged administration of corticosteroids results in drastic side effects that limit the therapeutic value of this class of anti-inflammatory agent.

Nonsteroidal anti-inflammatory agents (NSAIDs) are also utilized as a means to reduce effects associated with the inflammatory response. The principal pharmaceutical effects of NSAIDs are due to their ability to prevent COX activity resulting in the inhibition of prostaglandin

synthesis. Inhibition of prostaglandin synthesis by NSAIDs is anti-pyretic, analgesic, anti-inflammatory, and anti-thrombogenic. However, administration of NSAIDs may also result in severe side effects such as gastrointestinal bleeding, ulcers and incidence of renal problems. NSAIDs also inhibit both COX isoforms to varying degrees. For example, the most common NSAID, aspirin (acetylated derivative of salicylic acid), inhibits prostaglandin biosynthesis by irreversibly inactivating both COX-1 and COX-2 via acetylation of a serine residue located in the arachidonic acid binding domain. While aspirin inactivates both isoforms, it is 10 to 100 times more effective inactivating COX-1 as opposed to COX-2.

The selective inhibition of COX-2 has been shown to be anti-inflammatory and analgesic without the associated gastric and kidney related toxicity problems. This phenomenon is due to the discovery of NSAIDs that are capable of inhibiting COX-2, which is responsible for the production of prostaglandins that mediate the inflammatory response, without causing the inhibition of COX-1, which is responsible for the production of prostaglandins that maintain both gastrointestinal integrity, and kidney function. Thus, the beneficial effects of NSAIDs are separable from their drastic side effects by the development of COX-2 selective inhibitors.

Toward that end, several drugs that are COX-2 selective inhibitors of prostaglandin synthesis have been developed. The most extensively characterized class of COX-2 selective inhibitor is diarylheterocycles, which include the recently approved drugs celecoxib and rofecoxib. However, other classes include, but are not limited to, acidic sulfonamides, indomethacin analogs, zomepirac analogs, and di-*t*-butylphenols. For example, U.S. Pat. No. 5,380,738

describes oxazoles which selectively inhibit COX-2, U.S. Pat. No. 5,344,991 describes cyclopentenes which selectively inhibit COX-2, U.S. Pat. No. 5,393,790 describes spiro compounds which selectively inhibit COX-2, WO94/15932 describes thiophene and furan derivatives which selectively inhibit COX-2, and WO95/15316 describes pyrazolyl sulfonamide derivatives which selectively inhibit COX-2.

In order to afford an alternative to drug-based selective COX-2 therapy, it would be highly beneficial to provide nutraceuticals that inhibit COX-2, or even more preferably selectively inhibit COX-2. A nutraceutical, in this context, is an edible food or extracts therefrom that exhibit COX-2 inhibitory activity. In particular, it would be highly beneficial to obtain such edible food or extract from a plant source due to the ability to derive a large quantity of edible food or extract from a plant at a relatively affordable cost. These nutraceutical agents could be utilized in the diet in a preventative manner to maintain a "healthy" physiological state. The nutraceutical agents could also be used as a means to treat, cure or mitigate an existing inflammatory-related ailment either alone or in combination with another compound as a part of combination therapy.

Summary of the Invention

Among the several aspects of the invention therefore, is provided a method for selective inhibition of COX-2 in an organism, the method comprising the step of administering to the organism a therapeutically or prophylactically effective amount of an organic extract of an edible plant, wherein the inhibitory effect of the extract on COX-2 activity is greater than or equal to about 2 times greater than the inhibitory effect of the extract on COX-1 activity.

Another aspect of the invention is a method for inhibiting the activity of COX-2 in an organism, the method comprising the step of administering to the organism a therapeutically or prophylactically effective amount of an organic extract of an edible plant, wherein the plant is selected from the order consisting of Agavales, Apocynales, Arales, Aristolochiales, Asterales, Brassicales, Cactales, Caryophyllales, Cucurbitales, Elaeagnales, Fagales, Gnetales, Graminales, Lamiales, Liliales, Malvales, Musales, Myrtales, Papaverales, Plantaginales, Polemoniales, Ranales, Rosales, Rubiales, Rutales, Scrophulariales, Umbellales, Urticales, and Violales.

Still further is provided a method for selective inhibition of COX-2 in an organism, the method comprising the step of administering to the organism a therapeutically or prophylactically effective amount of an organic extract of an edible plant, wherein the inhibitory effect of the extract on COX-2 activity is greater than or equal to about 2 times greater than the inhibitory effect of the extract on COX-1 activity, wherein the organic extract is a purified composition obtained by a method comprising contacting the plant with an organic solvent to remove an extract from the plant wherein the extract inhibits COX-2 activity and then isolating the extract with COX-2 inhibitory activity.

In yet another aspect of the invention is provided a method of treating or preventing COX-2 mediated inflammation or an inflammation-associated disorder in an organism, the method comprising administering to the organism a therapeutically or prophylactically effective amount of a purified composition of an organic extract isolated from an edible plant wherein the purified composition is obtained by a method comprising contacting the plant with an organic solvent to remove an extract from the plant wherein the

extract inhibits COX-2 activity and then isolating the extract with COX-2 inhibitory activity.

Other features of the present invention will be in part apparent to those skilled in the art and in part pointed out in the detailed description provided below.

Brief Description of the Drawings

These and other features, aspects, and advantages of the present invention will become better understood with regard to the following description, appended claims and accompanying figures where:

Figure 1 depicts COX-2 > COX-1 inhibition by extract isolated from *Vitex agnus-castus*.

Figure 2 depicts COX-2 > COX-1 inhibition by extract isolated from *Citrus limonia*.

Figure 3 depicts COX-2 > COX-1 inhibition by extract isolated from *Citrus sp.*

Figure 4 depicts COX-2 > COX-1 inhibition by extract isolated from *Papaver somniferum*

Figure 5 depicts COX-2 > COX-1 inhibition by extract isolated from *Morus alba*

Figure 6 depicts COX-2 > COX-1 inhibition by extract isolated from *Abutilon sp.*

Figure 7 depicts COX-2 > COX-1 inhibition by extract isolated from *Coix lacryma*.

Figure 8 depicts COX-2 > COX-1 inhibition by extract isolated from *Artemisia dracunculus*.

Figure 9 depicts COX-2 > COX-1 inhibition by extract isolated from *Yucca elephantipes*.

Figure 10 depicts COX-2 > COX-1 inhibition by extract isolated from *Rumex japonicus*.

Figure 11 depicts COX-2 > COX-1 inhibition by extract isolated from *Dioscorea minutiflora*.

Figure 12 depicts COX-2 > COX-1 inhibition by extract isolated from *Capsicum annuum.*

Figure 13 depicts COX-2 > COX-1 inhibition by extract isolated from *Cissampelos mucronata.*

Figure 14 depicts COX-2 > COX-1 inhibition by extract isolated from *Cichorium endivia.*

Figure 15 depicts COX-2 > COX-1 inhibition by extract isolated from *Aster sp.*

Figure 16 depicts COX-2 > COX-1 inhibition by extract isolated from *Maranta arundinacea.*

Figure 17 depicts COX-2 > COX-1 inhibition by extract isolated from *Cynomorium sangaricum.*

Figure 18 depicts COX-2 > COX-1 inhibition by extract isolated from *Solanum tuberosum.*

Figure 19 depicts COX-2 > COX-1 inhibition by extract isolated from *Salvia sp.*

Figure 20 depicts COX-2 > COX-1 inhibition by extract isolated from *Stellaria media.*

Figure 21 depicts COX-2 > COX-1 inhibition by extract isolated from *Peucedanum sp.*

Figure 22 depicts COX-2 > COX-1 inhibition by extract isolated from *Asperula odorata.*

Abbreviations and Definitions

To facilitate understanding of the invention, a number of terms and abbreviations as used herein are defined below:

"Purified" means partially purified and/or completely purified. Thus, a "purified composition" may be either partially purified or completely purified.

"Extract" means crude extract, purified extract, and purified composition obtained by purification of the extract.

"COX activity" means the ability of either COX isoform,

COX-1 or COX-2, to catalyze the oxygenation reaction of arachidonic acid to PGG2.

"COX inhibitor or COX inhibition" means a composition, compound, agent or extract, purified or otherwise, that prevents either COX isoform, COX-1 or COX-2, from catalyzing the oxygenation reaction of arachidonic acid to PGG2 either in whole or in part.

"Selective inhibition of COX-2" means a composition, compound, agent, or extract, purified or otherwise, which selectively inhibits COX-2 activity over COX-1 activity as determined by the ratio of the percentage of COX-2 inhibition divided by the percentage of COX-1 inhibition, unless otherwise indicated herein.

"IC_{50}" means the concentration (in mol L^{-1}) that reduces a specified response to 50% of its former value. As used herein this value measures the amount of composition, agent or extract (ug extract/ml solvent) causing 50% inhibition of PGE2 production. The IC_{50} value may be used to determine COX-2 selectivity as specifically set-forth herein.

"Plant or parts thereof" means either the whole plant, or any part of the plant such as an aerial part, fruit, leaf, stem, or root and any combination thereof.

"Order", as utilized herein, is a taxonomic category of related organisms with a category consisting of a number of similar families.

"Family", as utilized herein, is a taxonomic category of related organisms ranking below the order and above the genus.

"Species", as utilized herein, is a fundamental taxonomic category ranking below a genus and consisting of a group of closely related individuals.

COX = the enzyme cyclooxygenase

COX-1 = the isoform cyclooxygenase-1

COX-2 = the isoform cyclooxygenase-2
NSAIDs = non-steroidal anti-inflammatory drugs
PGE2 = prostaglandin E2

Description of the Preferred Embodiment

Applicants have discovered that organic extracts of certain edible plants or parts therefrom inhibit COX-2 activity. Applicants have also discovered that organic extracts of certain edible plants or parts therefrom selectively inhibit COX-2 activity. The inhibitory effect is selective because inhibition of COX-2 is greater than inhibition of COX-1. Consequently, organic extracts of the edible plants or parts therefrom may be used to selectively inhibit the activity of COX-2 in an organism without causing an equivalent inhibition of COX-1 activity. Advantageously, these organic extracts are nutraceuticals that may be safely consumed and provide an alternative to traditional drug-based therapy for COX-2 inhibition.

Accordingly, the organic extracts of the present invention preferably inhibit COX-2 activity more than COX-1 activity. Preferably, the inhibitory effect of the plant extract on COX-2 is at least about two times greater than its inhibitory effect on COX-1. In a particularly preferred embodiment, the inhibitory effect on COX-2 is at least about 10 times greater than the inhibitory effect on COX-1. COX enzyme inhibition and selectivity may be determined in accordance with any method generally known to those of ordinary skill in the field, as set forth in more detail below.

In addition to inhibiting COX-2, the organic extracts of the present invention are preferably isolated from an edible plant. As utilized herein, the term "edible" shall generally mean a substance consumed for the purpose of

nourishment consisting of protein, carbohydrate (fiber or otherwise), fat and/or combinations thereof used in the body of an organism to sustain growth, repair and vital processes and to furnish energy. Classification of plants as edible versus non-edible, in addition to this general definition, is also based upon three primary criteria: (1) frequency of use as an edible substance; (2) availability in public commerce; and (3) toxicity limits due to potency. Therefore, the edible plant is preferably available to consumers in the region where the plant is provided in some form by lawful commerce. In addition, the edible plant preferably has a history of use which demonstrates that it may be safely consumed on a daily basis in amounts commonly employed in the indigenous culture where the edible plant is found for nourishment purposes. For example, a particular plant may be considered medicinal instead of edible if the plant is consumed by mouth for the purpose of correcting symptoms of illness (as opposed to nourishment) and is considered too potent to be consumed on a daily basis. Examples of edible plant uses include, but are not limited to: sources of starch, fruits, vegetables, spices, condiments, edible oils from plants, food coloring and other food additives, beverages, teas and tonics, sugar and other natural sweeteners, fermented beverages, ferments and enzymes, non-narcotic chewing leaves and gums, woody flavorings, and all other natural substances which are eaten or imbibed regularly to maintain health, sustain growth, repair injuries, and promote general well-being. In addition, any plant classified as edible by those of general skill in the art is included in the scope of the present invention, for example, such references include, NAPRALERT; Tyozaburo Tanaka, (Edited by Sasuke Nakoa) Tanaka's Cyclopedia of Edible Plants of the World, Keigaku Publishing

Co., Tokyo, Japan, 1976; Stephen Facciola, Cornucopia II: A Source Book of Edible Plants, Kampong Publications, Vista, California, 1998; James A. Duke, Database of Phytochemical constituents of GRAS Herbs and Other Economic Plants, CRC Press, Boca Raton, Florida, 1992; and George Macdonald Hocking, Dictionary of Natural Products, Plexus Publishing, Inc., Medford, New Jersey, 1997. The contents of these references are hereby incorporated in their entirety.

In a particularly preferred embodiment, organic extracts are isolated from edible plants of the following plant orders: Agavales, Apocynales, Arales, Aristolochiales, Asterales, Brassicales, Cactales, Caryophyllales, Cucurbitales, Elaeagnales, Fagales, Gnetales, Graminales, Lamiales, Liliales, Malvales, Musales, Myrtales, Papaverales, Plantaginales, Polemoniales, Ranales, Rosales, Rubiales, Rutales, Scrophulariales, Umbellales, Urticales, and Violales. The ability of extracts isolated from edible plants of these particular orders to inhibit COX-2, to selectively inhibit COX-2, and their use as edible plants are set-forth below in **Tables 1-24** and **Figures 1-22.**

It is to be understood that while applicant contemplates as within his invention the use of any organic extract isolated from edible plants wherein such extract inhibits COX-2 activity and preferably, wherein the inhibitory effect of such extract on COX-2 activity is greater than or equal to about 2 times greater than the inhibitory effect of the extract on COX-1 activity, that also included within applicant's contemplation are the use of such class or classes, but excluding any particular member(s) (e.g., species, genus or order) which may be previously disclosed and used and which inherently or otherwise possesses such required activity. For example, applicant's invention herein may include or exclude as

appropriate, the full scope of the invention as related to *Atractylodes lancea* as set forth in applicant's U.S. application ser. no. 09/272,363, which is fully incorporated herein by reference.

In order to prepare the organic extracts of the invention, an edible plant or parts thereof are preferably ground into a fine powder, the resultant powder is extracted with a solvent, and the extraction solvent is removed from the extract. The whole plant may be used or parts of the plant including an aerial part, fruit, leaf, stem, or root and any combination thereof may be utilized. If desired, the resultant extract may be further purified to yield a purified extract or one or more purified compositions. The grinding step may be accomplished by any commonly known method for grinding a plant substance. For example, the plant or parts thereof may be passed through a grinder to obtain a fine powder.

After the plant or parts thereof have been ground into a fine powder, they are combined with an extraction solvent. The solution is then stirred at a temperature, and for a period of time, that is effective to obtain an extract with the desired inhibitory effects on the activity of COX-2. The solution is preferably not overheated, as this may result in degradation and/or denaturation of compounds in the extract. The solution may be stirred at a temperature between about room temperature (25° C) and the boiling point of the extraction solvent. Preferably, the solution is stirred at about room temperature.

The length of time during which the plant powder is exposed to the extraction solvent is not critical. Up to a point, the longer the plant powder is exposed to the extraction solvent, the greater is the amount of extract that may be recovered. Preferably, the solution is stirred

for at least 1 minute, more preferably for at least 15 minutes, and most preferably for at least 60 minutes.

The extraction process of the present invention is desirably carried out using an organic solvent or a mixture of organic solvents. Organic solvents which may be used in the extraction process of the present invention, include but are not limited to hydrocarbon solvents, ether solvents, chlorinated solvents, acetone, ethyl acetate, butanol, ethanol, methanol, isopropyl alcohol and mixtures thereof. Hydrocarbon solvents which may be used in the present invention include heptane, hexane and pentane. Ether solvents which may be used in the present invention include diethyl ether. Chlorinated solvents which may be used in the present invention include dichloromethane and chloroform. Preferably, the solvent utilized for such extraction is a nonpolar organic solvent, such as dichloromethane or hexane.

The relative amount of solvent used in the extraction process may vary considerably, depending upon the particular solvent employed. Typically, for each 100 grams of plant powder to be extracted, about 500 ml of extraction solvent would be used. The organic solvent may be removed from the extract by any method known in the field of chemistry for removing organic solvents from a desired product, including, for example, rotary evaporation.

It is believed that the inhibitory effect of the plant extract of this invention on the activity of COX-2 is due to the presence of one or more compounds in the extract. Compounds present in the extract which inhibit the activity of COX-2 may be isolated and purified by those of ordinary skill in the art employing methods known in the art. For example, column chromatography and fractional distillation may be used to obtain pure compounds from the plant extract

of this invention.

The isolation and purification of particular compounds from the organic plant extracts of this invention may be performed as described in Resch, et al., J. Nat. Prod., 61, 347-350 (1998), the entire contents of which are incorporated by reference herein. The methods disclosed therein may be used to isolate and purify compositions which inhibit COX-2.

The ability of a particular organic extract to inhibit COX-1 or COX-2 is preferably determined by performing COX activity assays utilizing recombinant COX-1 and COX-2. The COX-1 and COX-2 genes may be subcloned from a variety of organisms, however in a preferred embodiment such genes are isolated from human or murine sources, using a variety of procedures known to those skilled in the art and detailed in, for example, Sambrook et al., Molecular Cloning, A Laboratory Manual, 2nd ed., Cold Spring Harbor Laboratory Press, (1989) and Ausabel et al., Short Protocols in Molecular Biology, 3rd. ed., John Wiley & Sons (1995). Additionally, the subcloned portion of the particular COX gene may be inserted into a vector by a variety of methods. In a preferred method, the sequence is inserted into an appropriate restriction endonuclease site(s) in a baculovirus transfer vector pVL1393 utilizing procedures known to those skilled in the art and detailed in, for example, Sambrook et al., *Molecular Cloning, A Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory Press, (1989) and Ausubel et al., *Short Protocols in Molecular Biology*, 3rd ed., John Wiley & Sons (1995).

The recombinant baculoviruses may be isolated by transfecting an appropriate amount of baculovirus transfer vector DNA into a sufficient quantity of SF9 insect cells along with linearized baculovirus plasmid DNA by the calcium

phosphate method or any other method generally know to those skilled in the art. (<u>See</u> M.D. Summers and G.E. Smith, *A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures*, Texas Agric. Exp. Station Bull. 1555 (1987)). Recombinant viruses may be purified by three rounds of plaque purification and high titer (10^7-10^8 pfu/ml) stocks of virus may be prepared.

Preferably, for large scale production, cells may be infected in approximately 10 liter fermentors (0.5×10^6/ml) with the recombinant virus stock such that the multiplicity of infection is greater than about 0.1. After several hours the cells are centrifuged and the cell pellet is homogenized in an appropriate buffer such as Tris/sucrose (50 mM/25%, pH 8.0). The homogenate may then be centrifuged at an appropriate speed and for an appropriate time (such as 10,000 × G for 30 minutes) so as to cause the homogenate to separate into a pellet and supernatant fraction. The resultant supernatant fraction will contain the desired product and may be stored at -80° C until use.

In order to test organic extracts for COX-2 inhibition and selectivity, standard COX-1 and COX-2 assays may be performed by employing ELISA procedures generally known to those skilled in the art. In such procedures, COX-1 and COX-2 activities are assayed as PGE_2 formed/μg protein/time using ELISA to detect the amount of PGE_2 synthesized from arachidonic acid. PGE_2 formation may be measured using PGE_2 specific antibody. Indomethacin, a non-selective COX-2/COX-1 inhibitor, may be employed as a positive control. The relative ability of various organic extracts to inhibit COX-1 or COX-2 at a particular concentration may be determined by comparing the IC_{50} value expressed as μg extract/ml solvent resulting in a 50% inhibition of PGE2 production. Selective inhibition of COX-2 may then be determined by the

IC_{50} ratio of COX-1/COX-2. Additionally, any other means to determine COX inhibition known to those generally skilled in the art may be employed, for example, determining the ratio of percent inhibition of COX-1/COX-2 at a fixed concentration of test agent.

The extracts of this invention may be used to manage, prevent and/or treat an organism having, or at risk for developing, a condition which is mediated in whole or in part by COX-2. Accordingly, conditions which may be benefited by inhibition of COX-2 or selective inhibition of COX-2 include, but are not limited to, the treatment of inflammation in an organism, and for treatment of other inflammation-associated disorders, such as, an analgesic in the treatment of pain and headaches, or as an antipyretic for the treatment of fever. For example, extracts of the invention would be useful to treat arthritis, including but not limited to rheumatoid arthritis, spondyloarthopathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis. Such extracts of the invention would be useful in the treatment of asthma, bronchitis, menstrual cramps, tendinitis, bursitis, skin-related conditions such as psoriasis, eczema, burns and dermatitis, and from post-operative inflammation including ophthalmic surgery such as cataract surgery and refractive surgery. Extracts of the invention also would be useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis, and treatment of cancer, including but not limited to the following types of cancer: colon, breast, prostate, bladder, or lung. In yet another preferred use, the extracts of the present invention may also be utilized as chemopreventive agents. Extracts of the invention would be useful in treating inflammation in such

diseases as vascular diseases, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, neuromuscular junction disease including myasthenia gravis, white matter disease including multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, nephritis, hypersensitivity, swelling occurring after injury, myocardial ischemia, and the like. The extracts would also be useful in the treatment of ophthalmic diseases, such as retinitis, retinopathies, uveitis, ocular photophobia, and of acute injury to the eye tissue. The extracts would also be useful in the treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis. Additionally, the extracts would be beneficial for the treatment of certain central nervous system disorders such as cortical dementias including Alzheimer's disease. The extracts of the invention are useful as anti-inflammatory agents, such as for the treatment of arthritis, with the additional benefit of having significantly less harmful side effects. These extracts would also be beneficial in the treatment of allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis and central nervous system damage resulting from stroke, ischemia and trauma. Additionally, the extracts would be useful in the treatment of pain, including but not limited to postoperative pain, dental pain, muscular pain, and pain resulting from cancer.

The present extracts may also be employed either alone or in combination with other compounds as a part of combination therapy, partially or completely, in place of other conventional anti-inflammatories. For example, such as together with steroids, NSAIDs, 5-lipoxygenase

inhibitors, leukotriene antagonists, LTA4 hydrolase inhibitors, and LTC4 synthase inhibitors. Preferably, with combination therapy, one will typically combine a drug or drugs and a nutraceutical, such as a plant extract of the current invention, in a manner such that the drug and the nutraceutical have different mechanisms of action, but yet target the same disease. For example, in a typical selection of agents for use in combination therapy to treat arthritis, one could utilize a plant extract of the present invention, which exhibits selective COX-2 inhibition with another agent known to attenuate inflammation associated with arthritis via an independent mechanism.

Those of ordinary skill in the art of preparing pharmaceutical formulations can readily formulate pharmaceutical compositions having plant extracts using known excipients (e.g., saline, glucose, starch, etc.). Similarly, those of ordinary skill in the art of preparing nutritional formulations can readily formulate nutritional compositions having plant extracts. And those of ordinary skill in the art of preparing food or food ingredient formulations can readily formulate food compositions or food ingredient compositions having plant extracts.

In addition, those of ordinary skill in the art can readily determine appropriate dosages that are necessary to achieve the desired therapeutic, prophylactic, pathologic or resuscitative effect upon oral, parenteral, rectal and other administration forms to the organism. Typically, *in vivo* models (i.e., laboratory mammals) are used to determine the appropriate plasma concentrations necessary to achieve a desired mitigation of inflammation related conditions.

The extracts of the present invention may be employed for the treatment and/or prevention of inflammation-related disorders, as identified above, in a number of organisms.

Besides being useful for human treatment, these extracts are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, avians, and the like. More preferred animals include horses, dogs, cats, sheep, and pigs.

The detailed description set-forth above is provided to aid those skilled in the art in practicing the present invention. Even so, this detailed description should not be construed to unduly limit the present invention as modifications and variation in the embodiments discussed herein can be made by those of ordinary skill in the art without departing from the spirit or scope of the present inventive discovery.

All publications, patents, patent applications and other references cited in this application are herein incorporated by reference in their entirety as if each individual publication, patent, patent application or other reference were specifically and individually indicated to be incorporated by reference.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

Examples

Sample Preparation

Plants or parts thereof were dried and sliced ("sample"). Samples of organic extracts were prepared from the edible plants listed in **Table 1.** The plant orders and families that the various samples were prepared from are also set forth in **Table 1**. In addition, details regarding the use of these plants as edibles is set-forth in **Table 2**. The particular sample was then ground into a fine powder using a coffee grinder. Approximately 100 grams of the resulting powder were added to approximately 500 ml of dichloromethane and stirred at room temperature for about 1 hour. The solvent was then removed by rotary evaporation, leaving several grams of the particular extract.

Inhibitory Effect of Various Plant Organic Extracts on COX-1 and COX-2 Activity

The particular extracts resulting from the sample preparation procedure detailed above were each evaluated for selective inhibition of COX-1 and COX-2. The COX-1 and COX-2 inhibition activities were determined in *vitro* according to the method of Gierse et al., *J. Biochem.*, 305, 479-484 (1995). This method is summarized below.

Preparation of recombinant COX baculoviruses

Recombinant COX-1 was prepared by cloning a 2.0 kb fragment containing the coding region of human or murine COX-1 into a BamH1 site of the baculovirus transfer vector pVL1393 (Invitrogen) to generate the baculovirus transfer vectors for COX-1 according to the method of D.R. O'Reilly et al., *Baculovirus Expression Vectors: A Laboratory Manual* (1992).

Recombinant baculoviruses were then isolated by transfecting 4 μg of baculovirus transfer vector DNA into (2 × 10^8) SF9 insect cells along with 200 μg of linearized baculovirus plasmid DNA by the calcium phosphate method. (See M.D. Summers and G.E. Smith, *A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures*, Texas Agric. Exp. Station Bull. 1555 (1987)). Recombinant viruses were purified by three rounds of plaque purification and high titer (10^7-10^8 pfu/ml) stocks of virus were prepared.

For large scale production, SF9 insect cells were infected in 10 liter fermentors (0.5 × 10^6/ml) with the recombinant baculovirus stock such that the multiplicity of infection was 0.1. After 72 hours the cells were centrifuged and the cell pellet was homogenized in Tris/sucrose (50 mM/25%, pH 8.0) containing 1% of 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate (CHAPS). The homogenate was then centrifuged at 10,000 × G for 30 minutes, and the resultant supernatant was stored at -80° C until use.

Recombinant COX-2 was prepared by cloning a 2.0 kb fragment containing the coding region of human or murine COX-2 in accordance with the same method described above for COX-1.

Assay for COX-1 and COX-2 Activities

COX-1 and COX-2 activities were assayed as prostaglandin E2 (PGE2) formed/μg protein/time using ELISA to detect PGE2 synthesized from arachidonic acid. CHAPS-solubilized insect cell membranes containing recombinant COX-1 or COX-2 enzyme were incubated in a potassium phosphate buffer (50 mM, pH 8.0) containing epinephrine, phenol, and heme. Compounds or extracts were pre-incubated

with the appropriate enzyme for approximately 10-20 minutes. Arachidonic acid (10 M) was then added to the mixture and the reaction was permitted to occur for ten minutes at room temperature (25° C).

Any reaction between the arachidonic acid and the enzyme was stopped after ten minutes by transferring 40 ml of reaction mixture into 160 ml ELISA buffer and 25 M indomethacin. Indomethacin, a non-selective COX-2/COX-1 inhibitor, was utilized as a positive control. The PGE_2 formed was measured by standard ELISA technology utilizing a PGE2 specific antibody (Cayman Chemical).

Approximately 200 mg of each extract obtained from the sample preparation procedure set-forth above were each individually dissolved in 2 ml of dimethyl sulfoxide (DMSO) for bioassay testing to determine the COX-1 and COX-2 inhibitory effects of each particular extract. Potency was determined by the IC_{50} value expressed as g extract/ml solvent resulting in a 50% inhibition of PGE2 production. Selective inhibition of COX-2 was determined by the IC_{50} ratio of COX-1/COX-2. The results of these bioassays performed utilizing extract isolated from the plant variety indicated are reported in **Tables 3-24** and **Figures 1-22** delineated below.

Table 1 below sets forth results of screening extracts of edible plants isolated from the orders, families, genera, and species indicated. A primary screen (indicated as 1° assay in Table 1) was performed in order to determine particular extracts that inhibit COX-2 at a concentration of 10 ug/ml. The extracts were then subjected to a confirmation assay to determine the extent of COX-2 inhibition at three different concentrations (10 ug/ml, 3.3 ug/ml and 1.1 ug/ml). The extracts were then tested for their ability to inhibit COX-1 at a concentration of 10

ug/ml. The percentage of COX inhibition compared to control is indicated as a percentage in each column, with a higher percentage indicating a greater degree of COX inhibition. In addition, the IC_{50} value for COX-1 and COX-2 was also determined for certain extracts as indicated in Table 1. The selectivity for these extracts was then determined by the IC_{50} ratio of COX-1/COX-2, as set-forth above. The COX-2 selectivity of extracts whose IC_{50} value was not determined may be calculated by dividing the percentage of COX-2 inhibition (at a concentration of 10 ug/ml) by the percentage of COX-1 inhibition (at a concentration of 10 ug/ml).

Table 1 -Extracts from Edible Plants that Inhibit COX-2

Order	Family	Genus	Species	Common name	Part	1° assay COX-2 (% inhib.) 10 ug/ml	Confirmation assay COX-2 (% inhib.) 10 ug/ml	3.3 ug/ml	1.1 ug/ml	COX-1 (% inhib.) 10 ug/ml	IC50 (ug/ml) COX-2	IC50 (ug/ml) COX-1	Selectivity COX-2/COX-1
Agavales	Agavaceae	Yucca	elephantipes	izote; Spanish dagger		88%	83%	46%	40%	15%	0.7	10	14
Apocynales	Asclepiadaceae	Asclepias	tuberosa	pleurisy root		82%	93%	**	17%	8%	***	***	***
Arales[9]	Araceae	Acorus	calamus	calamus root		76%	78%	57%	64%	39%	***	***	***
Arales[9]	Araceae	Acorus	gramineus	shih-chang	RT	91%	84%	52%	29%	53%	***	***	***
Arales[9]	Araceae	Colocasia	esculenta	malanga coco		77%	82%	46%	37%	21%	***	***	***
Arales[9]	Araceae	Colocasia	esculenta	taro	LF	76%	100%	**	30%	32%	***	***	***
Arales[9]	Araceae	Xanthosoma	sagittifolium	malanga	LF	87%	96%	**	31%	37%	***	***	***
Arales[9]	Araceae	Xanthosoma	sagittifolium	malanga	PT	76%	94%	**	27%	-82%	15	30	2
Aristocholiales	Aristolochiaceae	Aristolochia	unidentified			78%	89%	67%	49%	18%	***	***	***
Aristocholiales	Aristolochiaceae	Aristolochia	unidentified	radix aristolochiae	RT	75%	73%	54%	61%	10%	***	***	***
Asterales	Asteraceae	Artemisia	dracunculus	tarragon		77%	100%	**	31%	-6%	1.5	22	14.7
Asterales	Asteraceae	Aster	unidentified	Radix asteris	RT	79%	94%	**	36%	-1%	0.8	7.5	9.4
Asterales	Asteraceae	Blumea	alata			80%	69%	39%	39%	7%	***	***	***
Asterales	Asteraceae	Cichorium	endivia	endive		81%	100%	**	32%	13%	3.5	35	10
Asterales	Asteraceae	Crassocephallum	mannii			90%	100%	**	35%	24%	***	***	***
Asterales	Asteraceae	Silybum	marianum	milk thistle		85%	82%	75%	62%	23%	***	***	***
Asterales	Asteraceae	Sonchus	oleraceus	chicory		83%	83%	**	28%	4%	***	***	***
Asterales	Asteraceae	Taraxacum	mongolicum	mansen-tanpopo	PL	75%	100%	**	26%	36%	***	***	***
Asterales	Asteraceae	Taraxacum	officinale	dandelion		75%	86%	**	19%	-2%	***	***	***
Brassicales	Brassicaceae[2]	Brassica	rapa	turnip; choy sum		81%	86%	**	29%	27%	***	***	***
Brassicales	Brassicaceae[2]	Capsella	bursa-pastoris	shepherd's purse		86%	100%	**	30%	38%	***	***	***
Brassicales[1]	Brassicaceae[2]	Brassica	rapa	turnip		95%	85%	65%	39%	39%	***	***	***
Cactales	Cactaceae	Hylocereus	undatus	pitahaya	FL	76%	91%	65%	45%	43%	***	***	***
Caryothyllales	Amaranthaceae	Alternanthera	pungens	burweed		86%	81%	**	24%	23%	***	***	***
Caryophyllales	Caryophyllaceae	Stellaria	media	chickweed		80%	98%	**	21%	9%	2	15	7.5
Caryophyllales	Caryophyllaceae	Stellaria	media	chickweed		83%	94%	65%	78%	39%	4	20	5
Caryophyllales	Phytolaccaceae	Phytolacca	americana	pokeweed		80%	76%	58%	5%	-8%	***	***	***
Caryophyllales	Polygonaceae	Polygonum	aviculare	michi-yanagi		76%	81%	47%	28%	26%	***	***	***
Caryophyllales	Polygonaceae	Polygonum	caespitosum	hana-tade		78%	85%	46%	33%	30%	***	***	***
Caryophyllales	Polygonaceae	Polygonum	odoratum	knotweed; smartweed		78%	79%	60%	22%	37%	***	***	***
Caryophyllales	Polygonaceae	Polygonum	unidentified		PL	75%	76%	43%	55%	1%	***	***	***
Caryophyllales	Polygonaceae	Rumex	japonicus	Japanese dock		81%	100%	**	51%	3%	0.7	9	13.8
Cucurbitales	Cucurbitaceae	Citrullus	vulgaris	watermelon		87%	88%	89%	100%	47%	***	***	***
Cucurbitales	Cucurbitaceae	Mukia	maderaspatana	cucumber		88%	78%	**	30%	26%	***	***	***
Elaeagnales	Elaeagnaceae	Elaeagnus	umbellata	silver berry		82%	86%	81%	56%	50%	***	***	***
Fagales	Fagaceae	Castanea	sativa	Spanish chestnut	SD	79%	85%	83%	50%	51%	***	***	***
Gnetales	Ginkgoaceae	Ginkgo	biloba	ginko nuts		83%	100%	79%	53%	50%	***	***	***
Graminales	Poaceae[3]	Coix	lacryma-jobi	Job's tears		76%	81%	60%	29%	7%	2	35	17.5
Graminales	Poaceae[3]	Eleusine	coracana	sweet Indian millet	SD	84%	100%	**	48%	47%	***	***	***
Graminales	Poaceae[3]	Hordeum	distichum	barley		80%	100%	**	34%	30%	***	***	***

Table 1 -Extracts from Edible Plants that Inhibit COX-2

Order	Family	Genus	Species	Common name	Part	1° assay COX-2 (% inhib.) 10 ug/ml	Confirmation assay COX-2 (% inhib.) 10 ug/ml	3.3 ug/ml	1.1 ug/ml	COX-1 (% inhib.) 10 ug/ml	IC50 (ug/ml) COX-2	IC50 (ug/ml) COX-1	Selectivity COX-2/COX-1
Graminales	Poaceae[3]	Oryza	sativa	rice		78%	74%	54%	-20%	12%	***	***	***
Graminales	Poaceae[3]	Oryza	sativa var. sticky sweet	sticky sweet rice	SD	75%	95%	**	16%	20%	***	***	***
Graminales	Poaceae[3]	Zea	mays	corn		82%	85%	69%	49%	21%	***	***	***
Lamiales	Lamiaceae[4]	Lycopus	lucidus	herba lycopi	PL	75%	95%	**	15%	1%	***	***	***
Lamiales	Lamiaceae[4]	Ocimum	basilicum	herba ocimi	PX	75%	74%	40%	33%	21%	***	***	***
Lamiales	Lamiaceae[4]	Perilla	fructescens	folium perillae	LF	76%	82%	62%	31%	70%	***	***	***
Lamiales	Lamiaceae[4]	Prunella	vulgaris	spica prunellae	FL	78%	89%	**	26%	42%	***	***	***
Lamiales	Lamiaceae[4]	Salvia	unidentified	sage	RT	80%	94%	**	44%	62%	3.5	18	5
Lamiales	Verbenaceae	Vitex	agnus-castus	chaste lamb		82%	78%	47%	40%	0%	1.5	50	[illegible]
Liliales	Dioscoreaceae	Dioscorea	minutiflora	bush yam		79%	95%	**	17%	9%	1.5	18	12
Liliales	Dioscoreaceae	Dioscorea	unidentified	yam	RT	77%	59%	36%	-7%	-4%	***	***	***
Liliales	Liliaceae	Allium	schoenoprasum	Chinese chives		90%	96%	79%	46%	47%	***	***	***
Liliales	Liliaceae	Allium	unidentified		FR	77%	84%	**	20%	3%	***	***	***
Liliales	Liliaceae	Lilium	unidentified	lilly flower	FL	81%	91%	**	33%	23%	***	***	***
Liliales	Liliaceae	Smilax	ornata	sarsaparilla		79%	79%	**	-24%	3%	***	***	***
Liliales	Liliaceae	Trillium	erectum	bethroot		79%	72%	43%	55%	-5%	***	***	***
Malvales	Malvaceae	Abutilon	unidentified	mallow seed	SD	78%	96%	**	24%	-13%	1.5	28	18.7
Malvales	Sterculiaceae	Sterculia	lychnophora	luoi uoi	FR	81%	82%	58%	31%	45%	***	***	***
Musales	Marantaceae	Maranta	arundinacea	arrowroot		79%	100%	**	43%	-41%	0.7	5	7.7
Musales	Musaceae	Musa	paradisiaca	banana blossom	FL	82%	75%	49%	22%	21%	***	***	***
Myrtales	Balanphoraceae[10]	Cynomorium	sangaricum	caulis cynomorii	ST	83%	99%	**	41%	-12%	2	15	7.5
Myrtales	Onagraceae	Oenothera	biennis	primrose		78%	74%	52%	50%	14%	***	***	***
Papaverales	Capparidaceae	Capparis	spinosa	caper berries	FR	80%	86%	66%	33%	32%	***	***	***
Papaverales	Papaveraceae	Papaver	somniferum	poppy		80%	95%	90%	81%	65%	***	***	***
Papaverales	Papaveraceae	Papaver	somniferum	poppy	SD	87%	100%	**	47%	-8%	1.5	30	20
Papaverales	Papaveraceae	Papaver	somniferum	poppy	FL	79%	80%	60%	-42%	24%	***	***	***
Plantaginales	Plantaginaceae	Plantago	psyllium	psyllium		79%	76%	**	19%	18%	***	***	***
Polemoniales[7]	Boraginaceae[6]	Cordia	tetrandra			78%	80%	**	18%	23%	***	***	***
Polemoniales[7]	Convolvulaceae	Ipomoea	aquatica	water spinach		91%	79%	**	38%	29%	***	***	***
Polemoniales[7]	Solanaceae	Capsicum	annuum	pasilla Chile pepper	FR	76%	64%	32%	33%	37%	***	***	***
Polemoniales[7]	Solanaceae	Capsicum	annuum	pepper		83%	100%	**	69%	64%	0.75	8	10.7
Polemoniales[7]	Solanaceae	Capsicum	annuum	pepper		77%	73%	71%	24%	46%	***	***	***
Polemoniales[7]	Solanaceae	Capsicum	chinense	Chinese pepper	FR	84%	83%	69%	49%	37%	***	***	***
Polemoniales[7]	Solanaceae	Solanum	melongena	eggplant		80%	100%	**	65%	68%	***	***	***
Polemoniales[7]	Solanaceae	Solanum	tuberosum	potato		78%	100%	**	41%	45%	2	12	6
Polemoniales[7]	Solanaceae	Solanum	tuberosum	potato		76%	100%	**	31%	51%	***	***	***
Polemoniales[7]	Solanaceae	Solanum	tuberosum	potato		76%	72%	**	16%	5%	***	***	***
Ranales	Menispermaceae	Cissampelos	mucronata	jenjoko; mugulita		75%	99%	**	37%	20%	1.8	18	10

Table 1 -Extracts from Edible Plants that Inhibit COX-2

Order	Family	Genus	Species	Common name	Part	1° assay COX-2 (% inhib.)	Confirmation assay COX-2 (% inhib.)			COX-1 (% inhib.)	IC50 (ug/ml)	IC50 (ug/ml)	Selectivity
						10 ug/ml	10 ug/ml	3.3 ug/ml	1.1 ug/ml	10 ug/ml	COX-2	COX-1	COX-2/COX-1
Rosales	Fabaceae	Acacia	sieberiana	muwunga (Africa)		79%	49%	**	27%	9%	***	***	***
Rosales	Fabaceae	Albizzia	julibrissin	mimosa		82%	84%	64%	33%	41%	***	***	***
Rosales	Fabaceae	Glycine	max	soybean	SD	76%	89%	85%	53%	55%	***	***	***
Rosales	Fabaceae	Phaseolus	vulgaris var. Peruvian	Peruvian bean	SD	85%	67%	42%	18%	37%	***	***	***
Rosales	Fabaceae	Trigonella	foenum-graecum	fenugreek		76%	92%	**	25%	34%	***	***	***
Rosales	Fabaceae	Vigna	umbellata	red bean		79%	100%	**	32%	25%	***	***	***
Rosales	Fabaceae	Vigna	unguiculata	long bean	FR	78%	82%	58%	37%	61%	***	***	***
Rubiales	Rubiaceae	Asperula	odorata	woodruff		87%	90%	58%	72%	29%	1.5	4	2.7
Rubiales	Valerianaceae	Valeriana	officinalis	valerian root	RT	82%	100%	**	39%	57%	***	***	***
Rutales[1]	Rutaceae	Citrus	limonia	lime		84%	83%	**	29%	7%	1.5	35	[illegible]
Rutales[1]	Rutaceae	Citrus	unidentified			83%	93%	**	21%	12%	0.7	15	[illegible]
Scrophulariale	Acanthaceae	Acanthus	arboreus	otagalo		78%	44%	**	23%	11%	***	***	***
Umbellales	Apiaceae[5]	Angelica	sinensis	angelica; dong quai tea		76%	89%	87%	100%	52%	***	***	***
Umbellales	Apiaceae[5]	Carum	carvi	black caraway		92%	81%	83%	47%	53%	***	***	***
Umbellales	Apiaceae[5]	Centella	asiatica	gotu kola		75%	69%	**	30%	-119%	***	***	***
Umbellales	Apiaceae[5]	Eryngium	foetidum	coyote culantro; fitweed		90%	88%	62%	44%	35%	***	***	***
Umbellales	Apiaceae[5]	Peucedanum	unidentified		RT	78%	100%	**	33%	12%	0.9	4	4.4
Urticales	Moraceae	Morus	alba	fructus mori; gishi-gishi	FR	80%	88%	**	27%	5%	1	20	20
Urticales	Ulmaceae	Ulmus	rubra	slippery elm		75%	60%	31%	18%	28%	***	***	***
Violales	Flacourtiaceae	Pangium	edule	kluwak; pakem	FR	80%	90%	72%	55%	47%	***	***	***
Violales	Passifloraceae	Passiflora	edulis	passion flower	PX	86%	65%	45%	2%	-10%	***	***	***

* Primary screen performed at three concentrations. Samples were not repeated in a COX-2 confirmation assay.
** No data due to assay error.
*** Not tested.

[1]Brassicales also classified as Sapindales or Rutales
[2]Brassicaceae also classified as Cruciferae
[3]Poaceae also classified as Graminae
[4]Lamiaceae also classified as Labiatae
[5]Apiaceae also classified as Umbelliferae
[6]Boraginaceae also classified as Cordiaceae or Ehretiaceae
[7]Polemoniales also classified as Solanales
[9]Pandanales also classified as Arales or Alismatales
[10]Balanphoraceae also classified as Cynomoriaceae

The order, family, genus, and species of each plant whose extract was tested for COX-2 and COX-1 inhibitory activities are shown.

Table 2 below provides a description detailing the particular edible use of each plant extract tested for COX-2 inhibition as set-forth in **Table 1.** The plants are listed alphabetically according to genus. In addition, a comprehensive listing of references known to those generally skilled in the art is provided that details the edible consumption of these plants.

Table 2 - Edible Uses of Plant Extracts

Index	Scientific Name	Common Name	Isolate/ Chemical ID	Sample ID	Extract #	Reference
140	**Abutilon unidentified**	Mallows. Seeds edible.	78916	914485		
96	**Acacia sieberiana**	muwunga (African)	78486	914134		2
Yields a clear gum of good quality. Used like gum Arabic as bulking agent.						
1	**Acanthus arboreus**	otagalo	78487	914135		1,2
Leaves are a masticatory.						
17	**Acorus calamus**	calamus root	80328	922701		1,2,3,4
Rootstock made into candy. Also used as flavoring for alcoholic drinks.						
18	**Acorus gramineus**	Shih-chang	79050	914619		2
Rhizome is eaten.						
129	**Albizzia julibrissin**	mimosa	76892	912334		2
Young leaves are eaten after being boiled down.						
130	**Allium schoenoprasum**	Chinese chives	78569	914138		1,2,3,4
Leaves eaten in salads, soups and omelets.						
229	**Allium unidentified**	Many species edible.	79513	914847		
5	**Alternanthera pungens**	burweed	78470	914119		1,2
Young leaves are eaten.						

10	**Angelica sinensis**	angelica, Dong quai tea	79771	922605		3
Roots eaten in soups.						
31	**Aristolochia unidentified**	Leaves of *contorta* and *debilis* eaten boiled	79611	914945		
32	**Aristolochia unidentified**	Leaves of *contorta* and *debilis* eaten boiled	79611	915905		
35	**Artemisia dracunculus**	tarragon	78683	914252		3
Leaves eaten baked or in salads.						
34	**Asclepias tuberosa**	pleurisy root	80399	922772		1,2,3
Pods when boiled are eaten; tender shoots are eaten as greens. Roots are consumed boiled						
185	**Asperula odorata**	woodruff	80436	922809		1,2,3
This plant is used for flavoring a beverage.						
37	**Aster unidentified**	Young leaves of many species eaten.	78941	914510		
75	**Blumea alata**	Leaves of other species eaten.	78477	914125		
63	**Brassica rapa**	Choy sum	78573	914142		1,2,3,4
57	**Brassica rapa**	turnip	78567	914136		1,2,4
Roots are eaten fresh, grated, cooked, put in soup or pickled. Leaves are eaten.						
65	**Capparis spinosa**	Caper berries	79419	914753		1,2,3,4
Flower buds are eaten pickled.						
58	**Capsella bursa-pastoris**	shepherd's purse	80400	922773		1,2,3
The plant is used as a vegetable.						
206	**Capsicum annuum**	pepper	79789	922623		1,2,3,4
207	**Capsicum annuum**	pepper	78583	914152		1,2,3,4
212	**Capsicum annuum**	Pasilla Chile pepper	78624	914193		1,2,3,4
Pods and young leaves are edible.						
208	**Capsicum chinense**	Chinese pepper	78581	914150		6

The fruits are edible.						
12	**Carum carvi**	black caraway	78630	914199		1,2,3,4
Young shoots and leaves can be eaten. Seeds are used for flavoring.						
254	**Castanea sativa**	Spanish chestnut	78865	914434		1,2,3,4
fruits of most species edible						
13	**Centella asiatica**	gotu kola	78454	914103		1,2,3,4
The herb is eaten as a salad, also cooked in some countries.						
38	**Cichorium endivia**	endive	78703	914272		3
Leaves for salad or as a boiled vegetable.						
142	**Cissampelos mucronata**	jenjoko, mugulita	78485	914133		1,3
Cited for food use in NAPRALERT with no details.						
77	**Citrullus vulgaris**	watermelon	79763	922597		2
Fruits are eaten ripe. Seeds are parched and eaten.						
195	**Citrus limonia**	lime	78593	914162		3
The juice is used to add sour taste to foods. Also used in beverages.						
196	**Citrus unidentified**	Fruits of most are edible (oranges, limes, lemons, etc.)	77669	912496		
163	**Coix lacryma-jobi**	Job's tears	80461	922834		1,2,3
Seeds are used as tea in Japan, Vietnam, etc. They are eaten as cereals in porridge, soups or pastries						
22	**Colocasia esculenta**	Malanga coco	78076	912918		1,2,3,4
23	**Colocasia esculenta**	Dried taro stem	79794	922628		1,2,3,4
The tubers are eaten boiled, fried, steamed, put in soup (essential in New Year ceremonial miso-soup in W. Honshu), pounded into dumplings or employed as a starch resource. Young leaves and leaf stalks are eaten as vegetable or sun-dried for later use.						
86	**Cordia tetrandra**	Species not found, but the fruits of a number of species of this genus are edible.	77182	912455		
39	**Crassocephallum mannii**	Possibly Gynura	78469	914118		

		mannii. Species not found, but leaves of other species edible.				
82	**Cynomorium sangaricum**	Species not found. Other species are condiments.	79013	914582		
83	**Dioscorea minutiflora**	bush yam	78483	914131		6
Tubers (tubercules) are edible.						
84	**Dioscorea unidentified**	Yams. Most tubers edible	79323	914657		
249	**Elaegnus umbellata**	Silver berries	76938	912365		5
Fruits edible scalded.						
167	**Eleusine coracana**	Sweet Indian millet	79796	922630		1,2,3,4
Cereal grain eaten.						
14	**Eryngium foetidum**	coyote culantro; fitweed	78570	914139		1,2,3,4
Roots as condiment in soups and meat dishes they impart a very agreeable flavor. Young leaves are eaten raw, steamed or cooked with rice						
117	**Ginkgo biloba**	ginko nuts	78610	914179		3
Seeds (nuts) are edible roasted or dried.						
111	**Glycine max**	Soy bean	78995	914564		1,2,3,4
Bean is eaten.						
164	**Hordeum distichon**	barley	80506	922879		5
Cereal grain edible. Used in making beer.						
64	**Hylocereus undatus**	Pitahaya	78839	914408		2
Fruit is edible.						
76	**Ipomoea aquatica**	water spinach	78608	914177		1,2,3,4
Leaves and young, tubular stems are used as vegetable.						
134	**Lilium unidentified**	Lilies. Bulbs of many species edible.	79331	914665		
120	**Lycopus lucidus**	Herba Lycopi	79514	914848		2
Roots eaten boiled or in soup.						

141	**Maranta arundinacea**	arrowroot	78867	914436		3
Tubers are eaten raw, roasted, grated into a coarse meal or made into arrowroot powder.						
145	**Morus alba**	Fructus Mori	79019	914588		2,4
Fruits are edible (mulberry).						
78	**Mukia maderaspatana**	Alternate name is *Cucumis maderaspatana*. These are cucumbers. Most related species have edible fruit.	78458	914107		
147	**Musa paradisiaca**	Banana blossom	78578	914147		1,2,3
Fruit and blossoms are edible.						
121	**Ocimum basilicum**	Herba Ocimi	78971	914540		1,3,4
Basil is used as a flavoring.						
152	**Oenothera biennis**	primrose flowers	80412	922785		1,2,3
Roots and the shoot are eaten; the latter is consumed as salad.						
165	**Oryza sativa**	rice, many varieties	79428	914762		1,2,3,4
166	**Oryza sativa var. sticky sweet**	Sticky sweet rice	79796	922630		1,2,3,4
It is boiled or steamed usually, though some nations often cook it with other vegetable or put in soups. It is also made into cakes, pastries, puddings and starch, and also fermented into intoxicating beverages, vinegar and miso.						
228	**Pangium edule**	Peeled kluwak nut	79314	914648		2
154	**Papaver somniferum**	poppy	78646	914215		1,2,3,4
155	**Papaver somniferum**	poppy	78612	914181		1,2,3,4
156	**Papaver somniferum**	poppy	80445	922818		
Opium, one of the famous narcotics, is obtained from the milky juice of the capsule. In India, beverages are prepared from it. Nursery plant is eaten as vegetable in China. Seeds are used in sweetmeats, bakery food, confectionary, curries and the manufacture of an edible oil.						
157	**Passiflora edulis**	Passion flower	79382	914716		1,2,3
Fruit is edible.						
122	**Perilla fructescens**	Folium Perillae	78955	914524		5

Oil used in oriental cooking. Leaves are a flavoring.						
227	**Peucedanum unidentified**	Most species are medicinal, but leaves and tubers of some species edible.	78939	914508		
107	**Phaseolus vulgaris var. Peruvian**	Peruvian bean	79398	914732		1,2,3,4
Seeds and pods are edible.						
158	**Phytolacca americana**	pokeweed	80393	922766		1,2,3,4
Young shoots are eaten as potherb. Fruit was used to color wine and confectionaries.						
162	**Plantago psyllium**	psyllium seed	80408	922781		3
Sprouted seeds eaten in salads. Seeds yield nutritional oil. Seed husk mucilage used as thickener.						
268	**Polygonum aviculare**	Michi-yanagi	76896	912336		2,3,4
Leaves edible.						
269	**Polygonum caespitosum**	Hana-tade	76928	912358		5
Edible in soups						
170	**Polygonum odoratum**	knotweed, smartweed	78837	914406		1,2,3
A condiment for fish and meat.						
232	**Polygonum unidentified**	Many species edible.	79569	914903		
123	**Prunella vulgaris**	Spica prunellae	79018	914587		1,2,3,4
Cold-water infusion of the plant is a beverage						
173	**Rumex japonicus**	Japanese dock	76821	912284		1,2,3
Leaves are eaten boiled, in soups or dried for later use. Seeds are mixed with rice or ground into flour for making into dumplings.						
124	**Salvia unidentified**	Sages. Whole plant edible in most species.	79492	914826		
43	**Silybum marianum**	milk thistle tea	79480	914814		1,2,3,4
Young shoots are boiled and eaten in spring. Seeds are roasted into a coffee substitute.						
136	**Smilax ornata**	sarsaparilla	80404	922777		6
Used as a flavoring for beverages.						

214	**Solanum melongena**	eggplant	78835	914404		1,2,3,4
Fruit is cooked, put in soup, eaten raw with rice, stewed, fried, or-roasted, baked or pickled. One of the favorite culinary vegetables in the Far East. Leaves are mixed with the rice bran and salt.						
215	**Solanum tuberosum**	potato	79653	914987		1,2,3,4
216	**Solanum tuberosum**	potato	79654	914988		1,2,3,4
217	**Solanum tuberosum**	potato	79651	914985		1,2,3,4
Tubers are eaten in salad when raw. They are eaten cooked, steamed, fried, mashed, otherwise prepared into various dishes. They are an important staple food in many countries, also the essential source of starch and alcohol.						
44	**Sonchus oleraceus**	chicory	78466	914115		1,2,3,4
Young leaves are eaten raw or parboiled and then cooked.						
68	**Stellaria media**	chickweed	76809	912274		3
69	**Stellaria media**	chickweed	79762	922596		3
Young parts are used as boiled vegetable in time of scarcity.						
230	**Sterculia lychnophora**	Luoi uoi	78838	914407		2
Seeds are made into a beverage.						
47	**Taraxacum mongolicum**	Mansen-tanpopo	79523	914857		2.4
Leave eaten as boiled vegetable						
46	**Taraxacum officinale**	dandelion	79478	914812		1,2,3,4
Leaves are used in salads; sometimes bleached. Source of Dandelion wine. Roots are eaten raw, boiled or in lieu of coffee.						
110	**Trigonella foenum-graecum**	fenugreek seed	78605	914174		1,2,3,4
Seeds are used to adulterate coffee, also for spice. Leaves and pods are used as vegetable.						
137	**Trillium erectum**	bethroot	79018	914587		1,2,3,4
Young leaves are eaten in salads and as a potherb.						
225	**Ulmus rubra**	slippery elm bark tea	79479	914813		3
Powdered bark is edible. Sweet mucilaginous inner bard is chewed						
236	**Valeriana officinalis**	Valerian root	79365	914699		1,3,4
Root used to flavor ice cream, etc. Also used as an herbal tea.						
112	**Vigna umbellata**	red bean	78604	914173		1,3

Young leaves and pods eaten steamed. Dried seed boiled and eaten with rice and soups.						
113	**Vigna unguiculata**	long bean	78580	914149		1,2,3,4
Seeds are edible steamed, boiled or stir-fried. Dried seeds used in soups.						
273	**Vitex agnus-castus**	Chaste lamb	79481	914815		4
Fruits of most species edible.						
26	**Xanthosoma sagittifolium**	Malanga	78574	914143		1,2,3,4
27	**Xanthosoma sagittifolium**	Malanga	78575	914144		1,2,3,4
Tubers are eaten like taro.						
4	**Yucca elephantipes**	Spanish dagger; izote	77717	912504		3
Flowers and young stem tips are edible.						
169	**Zea mays**	corn	79625	914959		1,2,3,4
Major cereal crop.						

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Tables 3-24 further illustrate the ability of certain extracts isolated from the families identified in Table 1 to selectively inhibit COX-2. A total of six different

concentrations of the various extracts were tested for their ability to inhibit both COX-1 and COX-2. The IC_{50} value for COX-1 and COX-2 was also determined and a selectivity ratio was then calculated as set forth above. **Figures 1-22** are graphs that depict the data shown in **Tables 3-24** as indicated.

Table 3 - Extract isolated from *Vitex agnus-castus*

Amount of Extract (ug/ml)	COX-1 Activity Relative to Control	COX-2 Activity Relative to Control
100	33%	Not determined
33.3	62%	5%
11.1	Note determined	13%
3.70	78%	31%
1.23	88%	57%
0.41	98%	79%

IC_{50} (ug/ml) COX-1	IC_{50} (ug/ml) COX-2	COX-2 Selectivity Ratio
50	1.5	33.3

Table 4 - Extract isolated from *Citrus limonia*

Amount of Extract (ug/ml)	COX-1 Activity Relative to Control	COX-2 Activity Relative to Control
100	19%	Not determined
33.3	52%	Not determined
11.1	70%	Not determined
3.70	79%	22%
1.23	92%	51%
0.41	98%	69%

IC_{50} (ug/ml) COX-1	IC_{50} (ug/ml) COX-2	COX-2 Selectivity Ratio

35	1.5	23.3

Table 5 - Extract isolated from *Citrus sp.*

Amount of Extract (ug/ml)	COX-1 Activity Relative to Control	COX-2 Activity Relative to Control
100	16%	4%
33.3	37%	4%
11.1	Not determined	7%
3.70	67%	16%
1.23	80%	35%
0.41	88%	64%

IC_{50} (ug/ml) COX-1	IC_{50} (ug/ml) COX-2	COX-2 Selectivity Ratio
15	0.7	21.4

Table 6 - Extract isolated from *Papaver somniferum*

Amount of Extract (ug/ml)	COX-1 Activity Relative to Control	COX-2 Activity Relative to Control
100	26%	Not determined
33.3	46%	Not determined
11.1	65%	5%
3.70	67%	26%
1.23	81%	55%
0.41	88%	72%

IC_{50} (ug/ml) COX-1	IC_{50} (ug/ml) COX-2	COX-2 Selectivity Ratio
30	1.5	20.0

Table 7 - Extract isolated from *Morus alba*

Amount of Extract (ug/ml)	COX-1 Activity Relative to Control	COX-2 Activity Relative to Control
100	33%	5%
33.3	45%	9%
11.1	Not determined	9%
3.70	68%	20%
1.23	80%	44%
0.41	103%	71%

IC_{50} (ug/ml) COX-1	IC_{50} (ug/ml) COX-2	COX-2 Selectivity Ratio
20	1	20.0

Table 8 - Extract isolated from *Abutilon sp.*

Amount of Extract (ug/ml)	COX-1 Activity Relative to Control	COX-2 Activity Relative to Control
100	23%	Not determined
33.3	44%	5%
11.1	74%	7%
3.70	76%	35%
1.23	89%	54%
0.41	113%	82%

IC_{50} (ug/ml) COX-1	IC_{50} (ug/ml) COX-2	COX-2 Selectivity Ratio
28	1.5	18.7

Table 9 - Extract isolated from *Coix lacryma*

Amount of Extract (ug/ml)	COX-1 Activity Relative to Control	COX-2 Activity Relative to Control
100	14%	Not determined
33.3	51%	5%
11.1	Not determined	11%
3.70	100%	39%
1.23	95%	59%
0.41	105%	80%

IC_{50} (ug/ml) COX-1	IC_{50} (ug/ml) COX-2	COX-2 Selectivity Ratio
35	2	17.5

Table 10 - Extract isolated from *Artemisia dracunculus*

Amount of Extract (ug/ml)	COX-1 Activity Relative to Control	COX-2 Activity Relative to Control
100	27%	Not determined
33.3	41%	1%
11.1	66%	5%
3.70	81%	23%
1.23	82%	51%
0.41	90%	75%

IC_{50} (ug/ml) COX-1	IC_{50} (ug/ml) COX-2	COX-2 Selectivity Ratio
22	1.5	14.7

Table 11 - Extract isolated from *Yucca elephantipes*

Amount of Extract (ug/ml)	COX-1 Activity Relative to Control	COX-2 Activity Relative to Control
100	4%	Not determined
33.3	28%	3%
11.1	Not determined	11%
3.70	66%	32%
1.23	79%	56%
0.41	105%	80%

IC_{50} (ug/ml) COX-1	IC_{50} (ug/ml) COX-2	COX-2 Selectivity Ratio
10	0.7	14.3

Table 12 - Extract isolated from *Rumex japonicus*

Amount of Extract (ug/ml)	COX-1 Activity Relative to Control	COX-2 Activity Relative to Control
100	10%	1%
33.3	30%	3%
11.1	Not determined	5%
3.70	63%	15%
1.23	72%	35%
0.41	88%	62%

IC_{50} (ug/ml) COX-1	IC_{50} (ug/ml) COX-2	COX-2 Selectivity Ratio
9	0.65	13.8

Table 13 - Extract isolated from *Dioscorea minutiflora*

Amount of Extract (ug/ml)	COX-1 Activity Relative to Control	COX-2 Activity Relative to Control
100	Not determined	Not determined
33.3	18%	Not determined
11.1	69%	Not determined
3.70	90%	24%
1.23	95%	50%
0.41	109%	70%

IC_{50} (ug/ml) COX-1	IC_{50} (ug/ml) COX-2	COX-2 Selectivity Ratio
18	1.5	12.0

Table 14 - Extract isolated from *Capsicum annuum*

Amount of Extract (ug/ml)	COX-1 Activity Relative to Control	COX-2 Activity Relative to Control
100	16%	7%
33.3	26%	9%
11.1	41%	11%
3.70	72%	18%
1.23	99%	38%
0.41	112%	65%

IC_{50} (ug/ml) COX-1	IC_{50} (ug/ml) COX-2	COX-2 Selectivity Ratio
8	0.75	10.7

Table 15 - Extract isolated from *Cissampelos mucronata*

Amount of Extract (ug/ml)	COX-1 Activity Relative to Control	COX-2 Activity Relative to Control
100	9%	Not determined
33.3	35%	Not determined
11.1	58%	8%
3.70	72%	34%
1.23	83%	58%
0.41	98%	83%

IC_{50} (ug/ml) COX-1	IC_{50} (ug/ml) COX-2	COX-2 Selectivity Ratio
18	1.8	10.0

Table 16 - Extract isolated from *Cichorium endivia*

Amount of Extract (ug/ml)	COX-1 Activity Relative to Control	COX-2 Activity Relative to Control
100	9%	2%
33.3	51%	8%
11.1	Not determined	27%
3.70	93%	46%
1.23	98%	78%
0.41	104%	98%

IC_{50} (ug/ml) COX-1	IC_{50} (ug/ml) COX-2	COX-2 Selectivity Ratio
35	3.5	10.0

Table 17 - Extract isolated from *Aster sp.*

Amount of Extract (ug/ml)	COX-1 Activity Relative to Control	COX-2 Activity Relative to Control
100	Not determined	Not determined
33.3	17%	Not determined
11.1	Not determined	1%
3.70	66%	23%
1.23	78%	40%
0.41	90%	69%

IC_{50} (ug/ml) COX-1	IC_{50} (ug/ml) COX-2	COX-2 Selectivity Ratio
7.5	0.8	9.4

Table 18 - Extract isolated from *Maranta arundinacea*

Amount of Extract (ug/ml)	COX-1 Activity Relative to Control	COX-2 Activity Relative to Control
100	Not determined	Not determined
33.3	7%	Not determined
11.1	26%	Not determined
3.70	57%	10%
1.23	65%	34%
0.41	82%	60%

IC_{50} (ug/ml) COX-1	IC_{50} (ug/ml) COX-2	COX-2 Selectivity Ratio
5	0.65	7.7

Table 19 - Extract isolated from *Cynomorium sangaricum*

Amount of Extract (ug/ml)	COX-1 Activity Relative to Control	COX-2 Activity Relative to Control
100	7%	Not determined
33.3	31%	Not determined
11.1	57%	3%
3.70	75%	37%
1.23	74%	57%
0.41	84%	75%

IC_{50} (ug/ml) COX-1	IC_{50} (ug/ml) COX-2	COX-2 Selectivity Ratio
15	2	7.5

Table 20 - Extract isolated from *Solanum tuberosum*

Amount of Extract (ug/ml)	COX-1 Activity Relative to Control	COX-2 Activity Relative to Control
100	13%	7%
33.3	27%	14%
11.1	50%	19%
3.70	82%	31%
1.23	96%	62%
0.41	102%	86%

IC_{50} (ug/ml) COX-1	IC_{50} (ug/ml) COX-2	COX-2 Selectivity Ratio
12	2	6.0

Table 21 - Extract isolated from *Salvia sp.*

Amount of Extract (ug/ml)	COX-1 Activity Relative to Control	COX-2 Activity Relative to Control
100	15%	8%
33.3	27%	10%
11.1	64%	22%
3.70	85%	47%
1.23	95%	80%
0.41	107%	88%

IC_{50} (ug/ml) COX-1	IC_{50} (ug/ml) COX-2	COX-2 Selectivity Ratio
18	3.5	5.1

Table 22 - Extract isolated from *Stellaria media*

Amount of Extract (ug/ml)	COX-1 Activity Relative to Control	COX-2 Activity Relative to Control
100	13%	8%
33.3	27%	12%
11.1	71%	23%
3.70	82%	51%
1.23	99%	86%
0.41	126%	115%

IC_{50} (ug/ml) COX-1	IC_{50} (ug/ml) COX-2	COX-2 Selectivity Ratio
20	4	5.0

Table 23 - Extract isolated from *Peucedanum sp.*

Amount of Extract (ug/ml)	COX-1 Activity Relative to Control	COX-2 Activity Relative to Control
100	3%	1%
33.3	23%	5%
11.1	Not determined	12%
3.70	51%	25%
1.23	70%	41%
0.41	88%	69%

IC_{50} (ug/ml) COX-1	IC_{50} (ug/ml) COX-2	COX-2 Selectivity Ratio
4	0.9	4.4

Table 24 - Extract isolated from *Asperula odorata*

Amount of Extract (ug/ml)	COX-1 Activity Relative to Control	COX-2 Activity Relative to Control
100	Not determined	Not determined
33.3	1%	5%
11.1	28%	6%
3.70	52%	26%
1.23	68%	55%
0.41	74%	84%

IC_{50} (ug/ml) COX-1	IC_{50} (ug/ml) COX-2	COX-2 Selectivity Ratio
4	1.5	2.7

As illustrated by these data, the organic extracts isolated from the indicated edible plant inhibit COX-2. In fact, several of the extracts selectively inhibit COX-2 over COX-1 by greater than 10-fold. In view of the above, it will be seen that the several objectives of the invention are achieved and other advantageous results attained.